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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	14

DATE MAILED: 10/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,757	OWENS ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-10,12,13 and 21-42* is/are pending in the application.

4a) Of the above claim(s) *22-29 and 35-39* is/are withdrawn from consideration.

5)☒ Claim(s) *2 and 13* is/are allowed.

6)☒ Claim(s) *1,3,5-10,12,21 and 40-42* is/are rejected.

7)☒ Claim(s) *30-34* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

This is the First Office Action on the Merits of the application which is a 371 of PCT/US99/24972, filed 22 October 2003, and claims benefit of U.S. Provisional application 60/105,330 filed 23 October 2003. The preliminary amendments filed 17 April 2001 and 6 August 2002 have been entered.

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 12, filed 7 July 2003 is acknowledged. The traversal is on the ground(s) that examination of the claims in Groups I-IV would not create an undue burden on the examiner. This is not found persuasive because, as pointed out in the previous Office Action, the groups are directed to subject matter having separate status in the art. Thus examination of additional groups in a single application imposes an undue burden on the Office.

The requirement is still deemed proper and is therefore made FINAL.

Newly submitted claims 22-29 and 35-39 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: As set forth in the original restriction requirement, the elected invention is directed to an isolated polynucleotide comprising the sequence set forth as SEQ ID NO:1, which is a rat smooth muscle α-actin promoter/enhancer, or a fragment or complement thereof and a polynucleotide that hybridizes thereto under highly stringent conditions. Thus, the elected invention is directed to a nucleic acid having a specific structure. In contrast, the newly added claims are directed to a nucleic acid having the activity of conferring smooth muscle cell-specific expression wherein the structure of

said nucleic acid is limited only in that it is found in nature as part of a smooth muscle α-A gene promoter/enhancer or is limited to having the structure of a human smooth muscle α-A promoter. With respect to the broad claims, the claims clearly encompass subject matter that is distinct from the elected invention as there is no requirement for the structural limitations of the elected invention. With respect to the claims limited to comprising the structure of a human SM α-A promoter/enhancer, the structural limitations of the claims and the elected invention are mutually exclusive, as a nucleic acid comprising the structural limitations of the elected invention, by definition, would not have the structure of a human smooth muscle α-A promoter.

Since applicant has received an action on for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 22-29 and 35-39 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1-10, 12, 13, 21, 30-34 and 40-42 are under consideration.

Claim Objections

Claims 30-34 and 40-42 are objected to because of the following informalities: The claims depend from a non-elected base claim. Amending claims that depend directly from the non-elected claims such that they are proper independent claims would be remedial.

Claims 31-34, 41 and 42 are additionally objected to because the claims recite limitations by reference to figures. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and

where it is more concise to incorporate by reference. M.P.E.P. 2173.05(s). In the instant case, it would be more concise to refer to the claimed polynucleotides by SEQ ID NO.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 9, 10 and 40-42 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims at issue are directed to a genetically engineered host cell comprising an isolated polynucleotide comprising the rat smooth muscle α-actin promoter/enhancer. As the specification teaches that the isolated SM α-actin promoter might be comprised within a transgenic animal of any species (page 26, first full paragraph), the claims, interpreted in light of the teachings from the specification, reasonably encompass genetically engineered host cells of a transgenic animal wherein said animal includes a human. Thus, the claims embrace a genetically modified human, which is non-statutory subject matter. Amending the claims such that they are directed to an isolated genetically engineered host cell would be remedial.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The instant claim 3 is directed to an isolated polynucleotide that hybridizes under highly stringent conditions to the complement of the polynucleotide of claim 1. First, as the nucleic acid of claim 1 is claimed using open language, the nucleic acid comprises sequence that is not disclosed in the specification (i.e., those portions comprised by the polynucleotide that are not SEQ ID NO: 1). Claim 3 thus encompasses nucleic acids that hybridize to unspecified sequences, which sequences are clearly not described in the disclosure. Amending the claim such that it is directed to an isolated polynucleotide that hybridizes to SEQ ID NO: 1 would be remedial.

More substantially, the specification does not provide a limiting definition of "highly stringent conditions". Page 17, line 25, of the specification provides "exemplary conditions of high stringency" but does not set forth the metes and bounds of highly stringent conditions.

Thus, the claims encompass nucleic acids that hybridize to SEQ ID NO: 1 under conditions of unspecified stringency, which would encompass nucleic acids that are not described in the disclosure. Amending the claims to recite the hybridization conditions set forth on page 17, line 27, would overcome these grounds for rejection.

Claims 9, 10 and 40-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated genetically engineered host cell comprising an isolated polynucleotide comprising the rat SM α-A promoter/enhancer does not reasonably provide enablement for a genetically engineered host cell comprising an isolated polynucleotide comprising the rat SM α-A promoter/enhancer wherein said host cell is comprised within a transgenic animal and said rat SM α-A promoter/enhancer is operably associated with a heterologous sequence encoding other than an enzymatic or light emitting reporter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and breadth of the claims: The claims at issue are directed to a genetically engineered host cell comprising an isolated polynucleotide comprising the rat smooth muscle α-actin promoter/enhancer, which in some claims is further limited to being operably associated with a heterologous coding sequence. As the specification teaches that the isolated SM α-actin promoter might be comprised within a transgenic animal of any species (page 26, first full paragraph), the claims, interpreted in light of the teachings from the specification, reasonably encompass genetically engineered host cells of a transgenic animal. Thus, the claims embrace a transgenic animal of any species wherein the transgenic animal comprises the rat smooth muscle α-actin promoter/enhancer operably associated with a heterologous sequence encoding any polypeptide.

State of the prior art and level of predictability in the art: With respect to claims that broadly encompass any species of transgenic animal, the prior art teaches that the phenotype obtained with one species of genetically modified animal is not predictive of the same phenotype in another species. When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (Sigmund (2000) *Artrioscler. Thromb. Vasc. Biol.* 20:1425-1429, page 1425, paragraph 1). Further, transgene expression and the physiological consequences of transgene products are not always accurately predicted in transgenic mouse studies (Wall (1996) *Theriogenology* 45:57-68). Still further, the particular genetic elements required for optimal expression varies from species to species. Our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable

behavior (Wall; *supra*). These teachings demonstrate that success in obtaining a useful phenotype in one species of animal is not an accurate predictor of a useful phenotype in other species.

Next, the art generally teaches that the phenotype arising from insertion or deletion of even a well-characterized gene in a transgenic animal is highly unpredictable. Doetchman (1999) *Lab. Animal Sci.* 49:137-143 teaches, "[o]ne often hears the comment that genetically engineered mice...are not useful because they frequently do not yield the expected phenotype, or they don't seem to have any phenotype. These expectations are often based on years of work, and in some instances, thousands of publications of mostly in vitro studies" (page 137, paragraph 1). Doetchman goes on to teach, "it has become clear that genetic background plays an important role in the susceptibility of mice to many disorders. Therefore, the phenotypes of knockout mouse strains will also have genetic background dependencies" (page 140, column 2, third full paragraph) and "[a]pparent lack of phenotype more likely reflects our inability to ask the right questions, or our lack of tools to answer them" page 142, first paragraph. These teachings point out that the phenotype arising from any given mutation or genetic manipulation of a transgenic animal is highly unpredictable and in many cases cannot be revealed by routine experimentation. Thus the skilled artisan would not know how to use a transgenic animal comprising any given heterologous coding sequence without first engaging in empirical experimentation to make the animal and identify a useful phenotype.

Amount of direction provided by the inventor and existence of working examples: The instant disclosure provides general teachings regarding how to make transgenic mice (see especially Example 6.1.2, beginning page 47) and how to use mice comprising the rat smooth

muscle α-actin promoter/enhancer operably associated with a Lac Z reporter gene. However, the specification fails to address the unpredictability of the phenotype arising from the many genotypes encompassed by the claims for which no phenotype has been established and provides no teaching that would enable the skilled artisan to use the full scope of animals encompassed by the claims regardless of the genotype of the animal.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, given the art-recognized unpredictability of the phenotype arising from any given genotypic modification, the skilled artisan would have to resort to trial and error experimentation in order to uncover a useful phenotype associated with each of the different genotypes encompassed by the claims in each species of animal encompassed by the claims. Given the breadth of the claims and the absence of any guidance in the disclosure or prior art that would enable the skilled artisan to make or use embodiments of the claimed invention other than those reduced to practice, practicing the invention commensurate with the full scope of the claimed subject matter would clearly require undue experimentation.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 5, 7 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Blank *et al.* (1992) *J. Biol. Chem.*267:984-989 as evidenced by NCBI Online, Nucleotide Sequence Accession No. S76011 (gi:242241).

Blank *et al.* discloses an isolated nucleic acid comprising the sequence disclosed in the instant application as nucleotides 1912-2578 of SEQ ID NO: 1 (see especially the third full paragraph in the left column on page 985 and the attached sequence alignment). The sequence disclosed by Blank *et al.* comprises a transcriptionally active fragment of SEQ ID NO: 1 according to claim 1(a) and nucleic acids 2011-2605 of SEQ ID NO: 1 according to claim 1(b), as well as portions of other portions of SEQ ID NO:1 set forth in claim 1. Further, the nucleic acid of Blank *et al.* would hybridize under highly stringent conditions to the complement of the polynucleotide of claim 1 according to claim 3, would comprise the complement of the polynucleotide of claim 1 (i.e., is double stranded) according to claim 5, is comprised within a vector according to claim 7, and comprises a sequence identical to 20 contiguous nucleotides of the sequence set forth as SEQ ID NO: 1 according to claim 21. As the nucleic acid disclosed by Blank *et al.* meets all of the limitations of the instantly claimed nucleic acid, the claims are anticipated by Blank *et al.*

Claims 1, 3-12 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Shimizu *et al.* 1995, *J. Biol. Chem.* 270:7631-7643 as evidenced by Blank *et al.* (*supra*).

Shimizu *et al.* teaches an isolated nucleic acid comprising the region immediately 5' to the transcriptional start site of the rat smooth muscle α-actin gene, which Blank *et al.* teaches comprises the nucleic acid of claims 1, 3, 5, 7 and 21 (*Id.*). Shimizu *et al.* further teaches the said isolated nucleic acid operably associated with a heterologous sequence encoding a reporter gene according to the limitations of claims 6, 10 and 12, wherein said nucleic acid operably associated with a heterologous sequence encoding a reporter gene is comprised within a vector according to

claim 8 and within a genetically engineered host cell according to claim 9 (see especially Figure 1 and the caption thereto). As the nucleic acid and host cell disclosed by Shimizu *et al.* meets all of the limitations of the instantly claimed nucleic acid and host cell, the claims are anticipated by Shimizu *et al.*

Allowable Subject Matter

Claim 2 is allowed.

Claim 13 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms

Anne-Marie Falk
ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER